--Residues 181-217 Val Met Cys Asp Met Asp Tyr Arg Gly Gly Gly Trp Thr Val Ile Gln Lys Arg Ile Asp Gly Ile Ile Asp Phe Gln Arg Leu Trp Cys Asp Tyr Leu Asp Gly Phe Gly (designated as SEQ ID NO: 5),

Residues 324-353 Cys Ser His Leu His Asn Lys Thr Gly Trp Trp Phe Asn Glu Cys Gly Leu Ala Asn Leu Asn Gly Ile His His Phe Ser Gly Lys Leu (designated as SEQ ID NO: 6),

Residues 271-285 Phe Lys Met His Leu Gly Arg Tyr Ser Gly Asn Ala Gly Asp Ala (designated as SEQ ID NO: 7), and

Residues 222-234 Glu Phe Trp Leu Gly Leu Lys Lys Ile Phe Tyr Ile Val (designated as SEQ ID NO: 8).--

REMARKS

Claims 10, 11, 24, 25, 30 and 31 are pending in the application.

In response to the Examiner's objection regarding the amendment to the specification, Applicants have provided herein the correct page and line where the amendment should be entered. A version of the amendment showing the changes made to the specification is submitted in Exhibit A, and is accompanied by the amended paragraph, which is submitted on a new page.

Examiner's Position

In the Office Action dated 07/29/2002 the Examiner made the following rejections:

(1) Claims 10, 11, 24, 25, 30, and 31 were rejected under 35 U.S.C. §101 as assertedly not supported by a specific, substantial and credible utility, or a well-established utility; and

(2) Claims 10, 11, 24, 25, 30, and 31 were rejected under 35 U.S.C. §112, first paragraph, for asserted lack of enablement.

Applicants traverse each of these rejections as follows.

35 U.S.C. §101 Utility Rejection Should Be Withdrawn

The rejection under 35 U.S.C. § 101 should be withdrawn because the specification does describe a specific, substantial, and credible utility for the claimed polypeptides. As disclosed in the specification at least in Figure 1, and at page 4, lines 4-13, the claimed polypeptide is homologous to FGL2, which is a prothrombinase that belongs to the family of serine proteases, which have a well-established enzymatic utility.

On pages 3 and 4 of the Office action mailed 7/29/02, the Examiner states that "The identification of the protein of the present invention as a prothrombinase is based solely on its 37% homology to prothrombinase Fgl2. However, a search of the sequence database revealed an angiopoietin protein having 99.8% homology to the protein of the present invention (disclosed in WO 01/05825)" leading the Examiner to conclude that the asserted utility of the claimed polypeptides is not substantial because "... further research would be required to confirm the function and utility of the protein in light of its more significant homology to a protein of a differing function."

The Examiner's conclusion is based on the assumption that a given polypeptide can only possess a single function. This assumption is incorrect, because it is well known in the art that a protein may have more than one function (for example see: Krasnow and Adler, Development 120:1883-1893 (1994); Wehrle-Haller and Chiquet, J Cell Sci 106:597-610 (1993); Sourdive et al., Nucleic Acids Res 25:1476-1484 (1997)). Therefore, the fact that the claimed polypeptide has homology to a polypeptide that has an asserted function that is different from that of the claimed polypeptide does not preclude the claimed polypeptide from having an additional biological function, particularly when the alternative function is disclosed in a public database. Indeed, at page 4 of the Office Action, the Examiner admits that the next highest homologies are to polypeptides having asserted utilities as prothrombinases and angiopoietins. The fact that the claimed polypeptides share significant homology to proteins having two different functions underscores the possibility that the claimed polypeptide may indeed possess more than one function. It cannot be presumed that the claimed polypeptide does not

have prothrombinase activity solely based on the fact that its highest sequence similarity is to a protein to which an angiopoietin activity has been assigned.

The specification teaches that the claimed polypeptide is a prothrombinase that is most similar to the human fibrinogen-like protein 2 (Fgl2). Fgl2 was originally cloned from mouse cytotoxic T- lymphocytes, and was named "fibrinogen-like" because of the homology of its C-terminus to the beta and gamma chains of fibrinogen (Koyama et al., Proc Natl Acad Sci 84:1609-1613 (1987)). The human ortholog was cloned subsequently (Ruegg and Pytela, Gene 160:257-262 (1995)), and both the mouse and human proteins have been characterized, and shown to directly cleave prothrombin (Yuwaraj et al., Genomics 71:330-338 (2001); Chan et al., J Immunol 168:5170-5177 (2002); Levy et al., Am J Pathol 156:1217-1225 (2000).

Applicants hereto provide in Exhibit B evidence that the claimed polypeptide is a prothrombinase. Exhibit B is a ClustalW alignment that contains the sequence comparison of the polypeptide of SEQ DI NO: 4 with those of the human (AF 104015) and the mouse (NP 032039.1) Fgl2 proteins. In the alignment the residues of the conserved fibrinogen domain are in bold, the PROSITE motif fibrinogen beta and gamma chains C-terminal domain signature W-W-[LIVVMFYM]-x(2)-C-x(2)-[GSA}-x(2)-N-G present in the claimed polypeptide and in the human and mouse FGL2 prothrombinases is underlined, while the potential serine protease sites are indicated by the asterisks. The serine protease site that is required for enzymatic activity of the mouse and human prothrombinase, and the serine protease site that is predicted to be necessary for the catalytic function of the claimed polypeptide are highlighted. The alignment clearly exemplifies that the polypeptide of the invention contains the conserved SXXK motifs, and the fibrinogen domain in the C-terminal region present in mouse and human Fgl2 (Chan et al., 2002; Levy et al., 2000).

Unlike the serine proteases of the coagulation cascade that have a catalytic domain HDS, and belong to the serine protease clan SA, both the human and the mouse Fgl2 belong to the clan SE serine proteases, and have a catalytic site motif SXXK, where X is any amino acid (Barrett and Rawlings, Arch Biochem Biophys 318:247-250 (1995); Chan et al., 2002; Levy et al., 2000). The claimed polypeptide, the human and mouse

Fgl2 contain 3, 4, and 3 SXXK motifs, respectively. Studies employing site directed mutagenesis have established that serine 91 of the human Fgl2, and serine 89 of the mouse Fgl2 are required for catalytic activity (Chan et al., 2002; Levy et al., 2000), thus establishing that the second SXXK site is the functional prothrombinase site. The alignment clearly shows that the polypeptide of SEQ ID NO: 4 also contains SXXK sites, and that based on the positioning of this site relative to that of the human and mouse Fgl2, it is highly likely that serine 93 found in the second SXXK of the claimed polypeptide is required for its prothrombinase.

Therefore, the specification and the evidence presented and discussed above show that the claimed polypeptides have a substantial and credible utility, in addition to the well-established utility associated with serine protein enzymatic family. The utility of the polypeptide is also specific inasmuch that it is not a utility shared by all polypeptides. Furthermore, the utility is also real world because the direct prothrombinase activity plays a pivotal role in a variety of disease states, including viral induced fulminant hepatitis, and cytokine-induced fetal loss (Parr et al., J Virol 69:5033-5038 (1995); Ding et al., J Virol 71:9223-9230 (1997); Clark et al., J Immunol 160:545-549 (1998); Levy et al., 2000), and as such the polypeptides of the invention are potentially useful for developing therapies for such diseases. For example antibodies could be developed to correct or ameliorate these conditions, and the polypeptides could be used for the screening of agents that would antagonize the activity of the polypeptides in the same conditions. Indeed, scientists have shown that in mice neutralizing antibodies to Fgl2 prevent fibrin deposition and liver cell necrosis that lead to the lethality of hepatic viral infection ((Fung et al., J Biol Chem 266:1789-1795 (1991)), and prevent cytokine-induced fetal loss in which fibrin deposition is prominent (Clark et al., (1998)). The real world utility of the claimed polypeptides is also disclosed in the specification at least on page 6, line 26 to page 8, line 10.

In addition, the Utility Examination Guidelines state that "when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion." Fed.

Reg., Vol. 66. No. 4, January 5, 2001, p. 1096. If the Examiner has sufficient evidence to rebut such an assertion, and rejects the claims for lack of utility, then the burden shifts back to the Applicant to provide evidence supporting such a well-established utility.

Examiner has taken the position that "The art of predicting protein function based solely on limited amino acid sequence homology is highly unpredictable as evidenced by the art", citing Bork et al. (Nature Genetics 18:313-318 (1998)), Smith et al. (Nature Biotechnology 1222-1223 (1997)), and Doerks et al. (trends in Genetics 14:248-250 (1998)). The paper by Bork speaks largely to the need to resolve the present lack of continuously updated sequences, and the insufficient or erroneous functional assignment disclosed in the sequence databases. Bork states that "... while further improvements will certainly ensue, they (currently available methods) are already capable of extracting subtle but functionally relevant signals from protein sequences", and provides a checklist in Table 2 (pg 316) that will minimize the risk of missing important functional signals hidden in the protein sequence. The checklist includes the suggestion of not simply transferring functional information from the best hit. Bork also underscores the importance of reviewing the literature to retrieve important functional information (pg 317, col 1, middle paragraph).

It is evident from the discussion above that Applicants did not rely only on the function associated with the top hit disclosed in the database, and instead have performed many of the tasks suggested in Bork's checklist, including reviewing the literature, to assign a function to the claimed polypeptide.

The papers by Smith and Doerks speak to the problem of assigning incorrect biological functions because of misleading and incomplete annotations, inconsistent nomenclature, and the mistake of assigning a function to proteins that are highly homologous yet have different functions. Smith specifically teaches as an example of incomplete annotation that a bifunctional protein may be annotated by only one of its two functions (pg 1223, col 1, second paragraph). It is possible that the annotation that assigns the angiopoietin activity to the polypeptide that shares 99.8% homology with the claimed polypeptide is such an example of an incomplete annotation as described by Smith.

In the Office Action mailed on 4/19/2002, the Examiner found claims 10 and 11 to be allowable, and suggested amendments to the remainder of the pending claims that would have put such claims in condition for allowance. Applicants heeded to the Examiner's suggestions, and provided the amended claims in the response to the Office Action of 5/9/2002. In the present Office Action, dated 7/29/2002, the Examiner has rejected all the previously allowable claims based solely on a database hit, which could very likely be an incomplete annotation, and on the presumption that all proteins can have only one function.

In light of the evidence and remarks presented above, Applicants respectfully request that the rejection of the pending claims under §101 be withdrawn.

(2) **35 U.S.C. §112, First Paragraph, Rejections Should Be Withdrawn**

The Claims are Enabled Since the Claimed Sequences Have Utility

The rejection of claims 10, 11, 24, 25, 30 and 31 under 35 U.S.C. § 112, first paragraph, for asserted lack of enablement because the invention lacked a specific and substantial or a well-established utility should be withdrawn for the reasons discussed above with respect to utility.

The rejection of claims 10, 11, 24, 25, 30 and 31 under 35 U.S.C. § 112, first paragraph, because the specification did not enable one of skill in the art how to make and use the claimed invention should also be withdrawn. The Examiner disputes that polypeptides having 99% homology to the claimed sequences are enabled by the specification. Applicants respectfully disagree with the Examiner for the following reasons.

Undue experimentation would not be required for one of ordinary skill in the art to make minor modifications to SEQ ID NO: 4 or SEQ ID NO: 9 to produce polypeptides that are 99% homologous and that retain prothrombinase enzymatic activity. For example, one may remove a few amino acids of SEQ ID NO: 4 or SEQ ID NO: 9 or otherwise modify SEQ ID NO: 4 or SEQ ID NO: 9 by making conservative substitutions. In fact, this type of experimentation is quite routine as evidenced by publications showing

that others have generated mutants of prothrombinases tested them for activity (Levy et al., 2000; Chan et al., 2002). *In re Wands*, cited by the Examiner, states that even "a considerable amount of experimentation is permissible, if it is merely routine . . ." Wands, 858 F.2d 731, 737, 8 U.S.P.Q.2D 1400 (1988).

At the time the present application was filed, it was well known in the art that the clan SE of serine proteases comprise a catalytic site having the SXXK motif (Barrett and Rawlings, 1995). It was subsequently demonstrated that the Fgl2 protein contains such an SXXK active site, and the specific serine residue required for the catalytic function of the enzyme was identified in both the human and mouse proteins. Thus, one of ordinary skill in the art would know which regions are likely important for activity and thus should be mutated in a conservative manner initially.

The specification also provides specific guidance for generating fragments and variants. See, e.g., page 14, lines 1-22 and page 17, line 26 to page 18, line 9. Pages 14 and 35 describe the production of amino acid insertions, deletions and substitutions and page 14 states that "Guidance in determining which amino acid residues may be replaced, added or deleted without abolishing activities of interest, such as growth factor antagonist activity, may be found by comparing the sequence of the particular polypeptide with that of homologous human or other mammalian growth factor antagonist polypeptides and minimizing the number of amino acid sequence changes made in regions of high homology (conserved regions) or by replacing amino acids with consensus sequence." Page 14 further explains the structural and chemical basis for determining whether a substitution is conservative or non-conservative, advise beginning with changes of 1-5 amino acids in size, and state that "The variation allowed may be experimentally determined by systematically making insertions, deletions, or substitutions of amino acids in a polypeptide molecule using recombinant DNA techniques and assaying the resulting recombinant variants for activity." Page 27 provides further guidance on the location of and nature of mutations. Page 27, line 21 to page 23 line 15 furthers describe well known procedures for generating mutants, such as site-directed mutagenesis, PCR-based methods or cassette mutagenesis. A large variety of other procedures are known in the art. In addition, assays for determining prothrombinase activity are well known in the art (Chan et al., 2002; Fung et al., 1991).

As noted by the Examiner, the Wands factors to be considered are: (1) the breadth of the claims, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the quantity of experimentation necessary. In this situation, the state of the prior art and relative skill of those in the art at the time of filing was quite high inasmuch as the production of any number of mutations in any protein would have been quite routine, and the specification provides adequate direction and guidance on the types, location and number of mutations to begin experimenting with, and the relative breadth of the claims (e.g. 99% identity) is not so expansive that undue experimentation would be required to arrive at the claimed subject matter.

Applicants note that the Patent Office has recognized that these types of claims may be permitted (see Example 14 of the Training Materials for Interim Written Description Guidelines, which the Applicants recognize are directed to a distinct patentability requirement).

For these reasons, Applicants respectfully submit that it would require no more than routine effort for one of ordinary skill in the art to use well known procedures to create variants and to use known assays to measure the activity of those variants. The scope of claims 25 and 31 is thus enabled and Applicants request that this §112 rejection be withdrawn.

CONCLUSION

On the basis of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance, and a Notice of Allowance is respectfully requested as soon as possible. If there are any questions regarding these amendments and remarks, or if further discussion would expedite allowance of the claims, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

Date: November 26, 2002

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